

# Resource competition and within-host disease dynamics

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**The host organism is a complex mosaic of cell populations that requires adequate supplies of nutrients for maintenance, growth and proliferation. Because many nutrient requirements may be shared by host cells, pathogens and indigenous microflora, all these cells may potentially compete for growth-limiting resources. Ecological theory can explain some of the dynamics commonly seen in host-pathogen interactions; and mechanistic resource-consumer theory provides an instructive framework for viewing the disease process.**

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Pathogenesis can be viewed as an ecological process in which a pathogen colonizes and persists within the host, producing a population that is sufficiently numerous, active and spatially localized to exert a pathological effect<sup>1</sup>. Controls on nutrient availability may place disease-causing organisms at a competitive disadvantage within the host environment<sup>2,3</sup>, and the dynamics of these interactions are broadly consistent with resource-consumer theory<sup>4</sup>.

## Resource limitation and potential resource competition within the host environment

Many nutrients within hosts potentially limit pathogen growth, their identity and availability varying with pathogen type and the specific site of invasion and infection. Evidence of resource limitation and possible resource competition between host and pathogen crops up in the biomedical literature with surprising frequency. For example, nutrient limitation of pathogen growth has been suggested to occur in the mammalian oral cavity<sup>5</sup>, gut<sup>6</sup> and vagina<sup>7</sup>.

The supply of several key nutrients can strongly influence the outcome of infection<sup>2,3</sup>. For example, data from experimental and clinical medicine have conclusively shown host iron-supply to be an important determinant of the within-host dynamics of many diseases. Most microbial pathogens have high iron requirements for growth, and expression of their virulence factors is also tightly controlled by iron availability<sup>8</sup>, which is thought to modulate pathogen dynamics in periodontal<sup>5</sup>, gut<sup>9</sup> and vaginal infections<sup>7</sup>. Typically, a high iron-supply to the host leads to a poor prognosis<sup>10,11</sup>.

Conversely, maintaining an adequate supply of protein to the host is crucial to

its immunocompetence. Protein malnutrition has consistently been found to compromise the host's ability to repel infection<sup>12</sup>, and it has become evident that specific amino acids may be extremely important. For instance, glutamine – the most abundant amino acid in the body – is a major fuel for lymphocytes, fibroblasts and macrophages<sup>13</sup>. Glutamine frequently becomes 'conditionally essential' during an infection, when the supply rate from host intake and body stores fails to match cellular demands of the host's system; a high supplemental supply of glutamine can be very beneficial in reducing and delaying mortality in infectious diseases<sup>14</sup>. The supplies of other nutrients can also be important, as discussed below.

## Resource supply rates and resource competition theory

The above examples demonstrate the existence of strong effects of nutrient availability on the outcome of infection in hosts. However, the mechanisms are still not completely understood. We will not consider the extreme case of general host malnutrition, but instead focus on interactions between the host and pathogen under more normal nutritional conditions.

These nutritional interactions fit one of three general cases. In Case 1, the host state before infection defines a controlled nutritional habitat within which pathogen growth or exclusion occurs (Box 1). In Case 2, the pathogen competes directly for growth-limiting resources, either with members of the host's indigenous microflora (Fig. 1a), or with competing pathogens located within the host environment (Box 2). In Case 3, the pathogen competes directly for growth-limiting resources with identifiable sub-populations of host cells within the host (Box 3).

### Case 1: The host as an environment

An individual host provides the environment in which an invasive pathogen potentially grows (Box 1). One host strategy to repel invasions is to use its regulatory systems to create internal conditions that are unfavorable to the initial growth and proliferation of pathogens. One general strategy is to restrict availability of key nutrients such that the per capita birth rate of the pathogen is low. Another host strategy is to maintain high cell-loss rates for the pathogen, for instance, through the host's defense systems (including phagocytes, antibodies, the T-cell-mediated immune response, natural killer cells and complement<sup>15</sup>).

For a pathogen limited by a single key nutrient, the critically important determinant of invasion or exclusion is  $R^*$ , the resource concentration at which the pathogen's birth rate just balances its mortality. A pathogen may encounter mortality from phagocytes, natural killer cells; cytotoxic T cells and bacteriophage. Pathogens in the mouth, vagina and gastrointestinal tract are also susceptible to losses via flushing that are comparable to cell loss in a chemostat. If the concentration of available, required nutrients in the local environment can be reduced by the host to levels below the pathogen's  $R^*$ , the pathogen's net growth rate when rare is negative, and its population will go to extinction before serious deleterious effects of resource restriction or pathogen growth affect the host (see Box 1). In the simplest case, the per capita growth rate of the host itself (or its cell lineage) is not growth-limited by these resources, at least over the time scale of the bout of infection.

This general strategy appears to be at the core of iron-withholding, a major non-immune defense system that has evolved in vertebrates to protect them against pathogen invasions<sup>11,16</sup>. Vertebrates have developed elaborate mechanisms to withhold iron from invading pathogens while retaining their own access to it, and (with the possible exception of the urinary tract) this mechanism, theoretically, can protect most body sites against invasion<sup>11</sup>. A multi-faceted system deprives bacterial, fungal and protozoan invaders of this essential metal<sup>17</sup>. Under normal conditions, iron availability is controlled through binding to high iron-affinity proteins (e.g. transferrin, lactoferrin and ferritin), and the concentration of free ionic iron is reduced to extremely low levels at most sites of potential invasion<sup>17</sup>. Free iron in body fluids is usually held below  $10^{-12}\mu\text{M}$ , while gram-negative bacteria, in contrast, require *c.*  $0.3\text{--}1.8\mu\text{M}$  for growth<sup>8</sup>. If successful infection occurs, a series of additional mechanisms further exploit the invading pathogen's high-iron requirements.

(1) The concentration of free, unbound iron in body fluids and in disease sites is lowered further by sequestration in iron-binding proteins. (2) Non-heme iron is actively withdrawn from infected host cells. (3) The host synthesizes antibodies to some of the iron-repressed surface proteins of pathogen cells<sup>17</sup>. As a result of the demonstrated success of the iron-withholding system, iron-chelating drugs are increasingly being used as anti-infective agents in humans<sup>9,17</sup>.

### Case 2a: The host's indigenous microflora versus one pathogen

Direct resource competition *sensu strictu* may occur between the pathogen and components of the vertebrate host's indigenous microflora. For example, it is known that gut microflora have a strong antagonistic effect on invaders<sup>18,19</sup>. This protective effect has been exploited with success in animal husbandry<sup>20</sup> and in human medicine<sup>21</sup>.

The growth of pathogens within the vertebrate gut is determined by many factors, among which the specific composition of the intestinal flora looms large. Although the operative mechanisms are not fully understood, changes in the host's

### Box 1. The host as an environment for pathogen growth

The Monod relationship describes how nutrient availability ( $R$ ) may limit pathogen birth rate ( $\mu$ ) (Fig. 1a). Resource competition theory<sup>4</sup> suggests that the outcome of microbial competition is predicted by  $R^*$ , the steady-state resource concentration at which the pathogen's birth rate balances its mortality loss ( $m$ ) (Fig. 1a). If the local resource concentration is reduced to below  $R^*$ , the net growth rate of the pathogen will be negative, leading to exclusion from the host at steady state.

Multiple resources may limit pathogens. The transition from limitation from one interactive essential resource ( $R_1$ ) to a second ( $R_2$ ) is characterized by a curved region of resource interaction. The Zero Net Growth Isocline (ZNGI) for two such resources is illustrated in Fig. 1b for a hypothetical pathogen A. For resource supply points between the origin and ZNGI A,  $dN/dt < 0$ ; the pathogen declines towards extinction (resulting in an infection-free host). For supply points outside the ZNGI (e.g. point S),  $dN/dt > 0$ ; the pathogen increases until resource concentrations are reduced by cellular consumption to the ZNGI. The pathogen's resource consumption vector ( $C_A$ ) is shown<sup>4</sup> in Fig. 1b; equilibrium (solid circle) for the pathogen is reached when the  $C_A$  is opposite and equal in magnitude to the supply vector ( $U$ ). For ZNGI A, pathogen invasion proceeds, leading potentially towards a disease state.

If the pathogen's ZNGI moves diagonally outwards owing to increased mortality from host defenses (ZNGI A' in Fig. 1c), or if the supply point is altered by the host (point S' in Fig. 1d), the infection fails. Nutritionally compromised hosts may be unable to inflict sufficient mortality on pathogens to resist invasion, particularly if nutrients do not limit pathogen growth.

These processes take time to approach equilibrium. However, unlike terrestrial and aquatic ecosystems, where sudden changes in environmental conditions can alter or prevent trends towards competitive exclusion, the mammalian body is homeostatic, and therefore much more likely to allow competitive cell-cell interactions to go to completion<sup>9</sup>.

nutrient supply may influence the composition of intestinal microflora such that non-pathogenic species dominate. The protective role of the indigenous gut flora may reflect both exploitative microbial resource competition and microbial antagonism<sup>22</sup>.

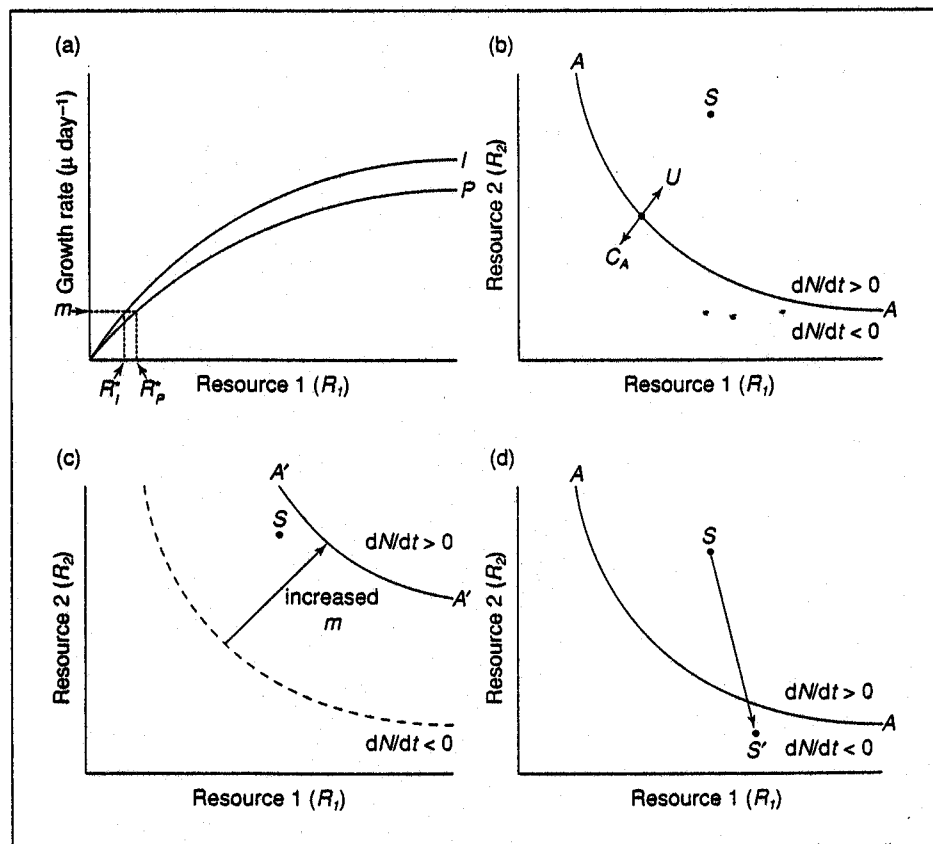
As shown in Fig. 1a, if the pathogen competes with components of the host's microflora for only one limiting nutrient, the pathogen (species P in Fig. 1a) will be eliminated if its  $R^*$  exceeds those of the host's competing microflora (species I in Fig. 1a). For the human gut pathogen *Clostridium difficile*, a principal limiting resource in the gut lumen may be carbon availability<sup>22</sup>. The concentration of carbohydrates within a chemostat colonized with mouse gut flora was insufficient to support the growth of *C. difficile in vitro*<sup>18</sup>, and the growth rate of *C. difficile* in filtrates from continuous cultures was increased by the addition of glucose and other carbon-containing substrates<sup>6</sup>.

For other pathogens, nutrients such as iron may be important. For example, infants that were fed breast milk without supplemental iron developed a gut flora comprising predominantly non-toxicogenic *Lactobacillus* species; infants fed iron-supplemented formula developed an intestinal flora that included toxicogenic bacteria such as *Clostridium*, *Salmonella* and *Staphylococcus*<sup>9</sup>.

Where key indigenous microbes have low abundances, pathogen control by indigenous microflora can be enhanced by the introduction of novel populations of non-pathogenic competitors. For example, the oral administration of 'competitive exclusion bacteria' can reduce gut colonization by the pathogen *Campylobacter jejuni* in poultry<sup>23</sup>, and, in humans, the administration of *Lactobacillus* GG is efficacious in terminating relapsing *Clostridium difficile* colitis<sup>21</sup>.

### Case 2b: Competition between two pathogens

Direct competition may occur between pathogens within the host environment



**Fig. 1.** (a) Resource-dependence of the birth rate of organisms growing on a single resource<sup>4</sup>, according to the Monod model, showing the values of  $R^*$  for both an indigenous microbe (I) and a pathogen (P) growing at a common mortality rate ( $m$ ).  $R^*$  is the steady-state resource concentration at which the pathogen's birth rate balances its mortality loss. I is the Monod curve for the indigenous microbe, and P is the Monod curve for the pathogen. (b) Zero Net Growth Isocline (ZNGI) for hypothetical species A growing on two interactive essential resources<sup>4</sup>, showing the consumption vector ( $C_A$ ), supply vector ( $U$ ) and resource supply point (S). (c) Effect of an increase in mortality rate ( $m$ ) on the location of the ZNGI for hypothetical species A. (d) Effect of a change in the location of resource supply point S on the growth rate of species A.

## Box 2. The host as an arena for competition between the pathogen and host-associated cells or between pathogens

The host can exploit its indigenous microflora as competitive weapons against invading pathogens. For example, a species of the host's indigenous microflora,  $I$ , outcompetes a pathogen species,  $P$ , for a single resource,  $R_1$ , if  $R^* < R^*_p$  (see Fig. 1a), where  $R^*$  is the resource concentration at which the pathogen's birth rate just balances its mortality.

The outcome of competition for multiple resources can be predicted graphically if ZNGIs (see Box 1), consumption vectors and resource supply points are known, both for experimental communities in the laboratory and for some natural communities, which are much more spatially and temporally complex<sup>4</sup>. There are two important scenarios.

(1) The ZNGIs for competing species may not intersect. If the ZNGI for one species is nearer the origin and wholly inside the ZNGIs of its competitors then that species is competitively superior for all supply points lying beyond its isocline, because its  $R^*$  values are lower than the values for its competitors.

(2) Alternatively, ZNGIs may cross. Because of phenotypic trade-offs, a competitively superior species for one resource typically will not be competitively superior for other resources<sup>4</sup>. Such trade-offs can cause ZNGIs to cross, creating a two-species equilibrium at their intersection. If each species consumes proportionately more of the resource that limits its own growth, this equilibrium is stable<sup>4</sup>. Crossing ZNGIs produce regions of exclusion and dominance (Fig. 2). For supply points in Region 1, insufficient resources are available to support either population ( $m > \mu$ ). For supply points in Regions 2 and 3, both will be Resource 1-limited ( $R_1$ ); species  $A$  will win by virtue of its lower  $R^*_1$ . For supply points in Regions 5 and 6, both will be limited by Resource 2 ( $R_2$ ), and species  $B$  will win. In Region 4, both species will coexist because  $A$  is limited by Resource 2, and  $B$  is limited by Resource 1. The relative biomass of species  $A$  and  $B$  will depend on the  $R_2:R_1$  supply ratio. For supply points along the diagonal gradient across Region 4, the relative biomass of species  $A$  will decline monotonically with a decrease in  $R_2:R_1$ . If the supply rate is increased ( $S_3$ ), the total biomass of both species will increase. By manipulating resource supplies, the host can potentially determine who wins this internal competitive struggle.

when the host is infected simultaneously by multiple pathogens. Direct pathogen-pathogen competition is especially relevant to the important medical problem of antibiotic resistance. Because of phenotypic trade-offs (Box 2), antibiotic-resistant bacterial strains should be competitively inferior to non-resistant strains. Goldhaber<sup>24</sup> proposed that if a host infected by an antibiotic-resistant pathogen (strain  $P_r$ ) was deliberately superinfected with a wild type or non-virulent pathogen ( $P_w$ ), the antibiotic-resistant strain could be out-competed *in vivo* by the wild type. A similar procedure has been used successfully to treat microbial infections in plants; inoculation with an atoxigenic strain of *Aspergillus flavus* resulted in the competitive displacement of a toxigenic *Aspergillus* infecting cotton bolls<sup>25</sup>.

The success of deliberate microbial superinfections could be enhanced by manipulating the host's nutritional supply so as to maximize the probability that strain  $P_r$  ( $A$  in Fig. 2) is competitively excluded by  $P_w$  ( $B$  in Fig. 2) (see Box 2). Once the resistant strain is successfully excluded, both antibiotic therapy and nutritional manipulation could then aim at eliminating the antibiotic-sensitive strain. Mathematical models of simultaneous pathogen infections have been developed<sup>26</sup>, and modifications of these models to incorporate explicit nutrient dependence of pathogen growth rate could provide insights into the nutritional conditions that facilitate superinfection therapy.

### Case 3: Host cell sub-populations versus one pathogen

Sub-populations of host cells may also compete with a pathogen for shared limit-

ing resources, in a fashion quite reminiscent of two species competing (Box 3). In this case, the host itself is an active and explicit competitor; sub-populations of its cells can respond via resource-driven changes in their own population size, including extinction. In contrast to the host simply defining an environment for pathogen dynamics (Case 1), sub-populations of host cells in Case 3 respond dynamically over time scales that are similar to those of the pathogen.

Host cellular sub-populations that may compete directly with pathogens for nutrients include cells of the immune system. Nutrients play a direct role as cofactors and regulators of the immune system<sup>27</sup>. For example, although macrophages are terminally differentiated cells that have lost the capacity to divide, they are extremely active metabolically and have a high demand for the amino acid glutamine; because they cannot synthesize glutamine, macrophages are dependent on extracellu-

lar sources<sup>13</sup>. In addition, both killer-cell activity and lymphocyte population responses are influenced by nutrient availability<sup>27</sup>. If a competing pathogen were to draw critical limiting nutrients away from immune cells, this strategy would support its own growth needs and also indirectly reduce a primary source of its own mortality within the host.

Indeed, in addition to cells of the immune system, all other host cells require resources for maintenance and growth; it is probable that these requirements are dramatically altered by infection with intracellular pathogens. Infected and non-infected sub-populations of host cells could compete with each other for limiting resources – if so, changes in nutrient supply ratios to the host could alter the competitive balance between them<sup>3</sup>. A shift is predicted from pathogen dominance (a fatal infection), to coexistence (persistent infections of decreasing degrees), to exclusion of the infected cells by the non-infected host cells, along a decreasing  $R_2:R_1$  supply ratio gradient from supply point  $S_1$  to supply point  $S_2$  (see Fig. 2). This mechanism may underlie the results of Peck *et al.*<sup>28</sup> (see Box 3). Resource competition between infected and non-infected cells may also be involved in nutritional effects on the progress of HIV infections<sup>3</sup>, and such results could have profound implications for the clinical management of illness.

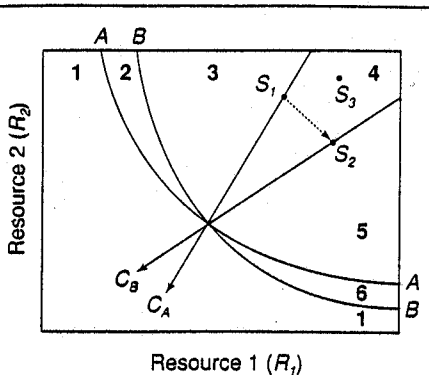
### Spatial and temporal heterogeneity

The outcome of resource competition in general is known to be strongly affected by environmental heterogeneity. Such heterogeneity surely modulates within-host competition as well. If a typical bacterium were scaled up to the size of a human host, the host would be larger than North America. From the bacterium's perspective, this vast host environment is characterized by substantial spatial and temporal heterogeneity in resource availability, mortality, and indigenous

## Box 3. Resource competition between the pathogen and host cell sub-populations

Consider a pathogen-infected sub-population of host cells ( $A$  in Fig. 2) that competes with a non-infected sub-population of the same host-cell type ( $B$  in Fig. 2) for two potential limiting resources  $R_1$  and  $R_2$ . Direct resource competition between two such sub-populations may help account for the results of Peck *et al.*<sup>28</sup>, who varied carbohydrate and casein availabilities (equivalent to resources  $R_2$  and  $R_1$  in Fig. 2) in a mouse model of infection by the intracellular pathogen *Salmonella typhimurium*. Both resources were provided in the diet in a range of carbohydrate:casein ratios, and the total resource supply was varied from low (see triangles in Fig. 3) to high (see squares in Fig. 3).

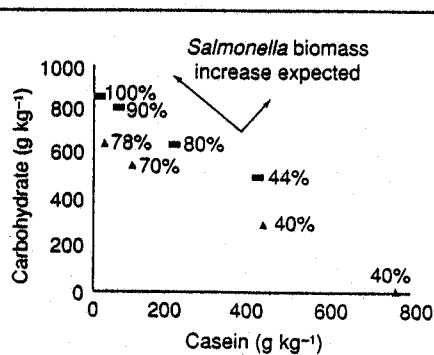
Although they found no correlation between observed mortality rates and concurrent immune function assays, dramatic changes in mortality occurred across the carbohydrate:casein supply ratio gradient. Under conditions of strong protein restriction (high carbohydrate:casein supply ratios), mouse mortality was very high; however, the mortality rate dropped dramatically as the carbohydrate:casein supply ratio was decreased in their diet (Fig. 3). Moreover, when the resource supply rate was increased (thus supporting a higher pathogen biomass; see Box 2), mortality increased at each supply ratio. This example suggests that resource supply could control the outcome of competition between sub-populations of infected and non-infected host cells.



**Fig. 2.** Zero Net Growth Isoclines (ZNGIs) for two hypothetical species A and B competing for two interactive essential resources, showing regions of exclusion (Regions 1–3, 5 and 6) and competitive coexistence (Region 4). In Region 4, the relative biomass of species A decreases linearly from 100% at supply point  $S_1$  to 0% at supply point  $S_2$  (see Box 2).

microflora. We cannot fully discuss here the implications of within-host heterogeneity for disease dynamics, but several basic points are important to note.

First, a pathogen's ability to invade and persist in the host may be determined in part by its strategies for dealing with these heterogeneities. A pathogen can withstand temporally transient stresses (e.g. nutrient deprivation) by entering a resting stage (e.g. spores), with later release cued by favorable changes in the host environment. Pathogens can exploit spatial heterogeneity via the vascular and lymphatic systems, which provide a ready, rapid-transit system for movement within the host. In case of trauma or nutrient depletion, intestinal *Escherichia coli* may penetrate the protective inner-gut lining, enter the blood stream, and move to favorable habitats throughout the host; devastating illness can ensue<sup>29</sup>. The host, in turn, may rely upon spatial heterogeneity to counter infection: likely initial sites of entry for potential pathogens should exhibit predictably unfavorable resource



**Fig. 3.** Effects of an oral carbohydrate:casein supply ratio gradient on the percent mortality experienced by mice three weeks after experimental injection with the intracellular pathogen *Salmonella typhimurium*<sup>28</sup> (see Box 3).

supply rates, be the focus of sustainable attack by components of the immune system, or harbor particularly antagonistic indigenous microflora.

## Conclusions

Williams and Nesse<sup>16</sup> noted the need for a theoretical framework based in ecology and evolution for interpreting the host–pathogen conflict, and significant advances are being made<sup>30–33</sup>. We argue here that resource–consumer theory provides a valuable and insightful conceptual framework for analyzing host–pathogen interactions. We have reviewed how nutrient supplies influence disease dynamics within vertebrate hosts, and suggest that the available evidence is tantalizingly consistent with the predictions of this body of theory<sup>2–4</sup>. However, much is yet to be learned about the resource dimensions of infectious diseases, including key nutrient requirements for pathogens and the internal availability of these nutrients within the host environment. Medical research and practice will be enriched, we hope, by viewing the internal struggle between hosts and pathogenic invaders through the lens of resource–consumer theory.

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